REMARKS:

In the Office Action dated March 10, 2006, claims 1-4 and 6-10, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-4 and 6-10 remain in this application, claim 5 has been withdrawn and new claims 11 to 13 have been added to the application.

The office action requests that the specification be amended to update the cross reference to related applications. The specification has been amended as requested.

Claims 1-4 and 6-10 were rejected under 35 USC §112, first paragraph as lacking enablement. The claims have been amended to indicate that the monomer protein induces differentiation of osteoblasts as measured by alkaline phosphatase activity. In addition, applicants point out that a lot of information was present in the state of the art with regard to the dimer MP52 and in particular dimer members of the BMP protein family, which is a subfamily of the TGF-β superfamily. Dimer members of the BMP protein family, including MP52, are characterized by common structural features, thus, changes in activity based on changes in the common structural features, are predictable among these proteins. For example, it was known to a skilled person that the members of this protein family are expressed as precursor proteins from which the mature protein is separated. It was also known that N-terminal ends can be shortened without changing the activity of these mature proteins (WO 89/09788). Thus, one skilled in the art would reasonably expect that fragments of SEQ ID NO:2, which are shortened at the N-terminus, would have the desired activity. This activity can easily be determined by measuring the

differentiation of osteoblast cells by means of the well known alkaline phosphatase assay (ALP). Therefore, the activity was not only expected due to the knowledge of the state of the art, but could also easily be determined.

WO 89/09788 (mentioned above) describes structural features and homologies of osteogenic proteins (item 2 of the Abstract) to which the BMP proteins, as typical members of the TGF-β superfamily, belong. WO 89/09788 describes how artificial sequences for proteins can be derived which exhibit cartilage and bone activity (item 4 of the Abstract). Examples for artificial sequences, which are derived from the structure of other members of the TGF-β family are shown on page 7 at the bottom (COP5, COP7, COP16). In two of these artificial osteogenic proteins, the first 5 amino acids of the 7-cysteine region are missing, however, they nevertheless retain activity. The derived generic sequences of artificial osteogenic proteins having cartilage and/or bone inducing activity, contain in correspondence with said findings only the conserved 7-cysteine region or are 5 amino acids shorter, i.e. they contain only 6 cysteines (see page 9 and 10 as well as page 24, middle to page 28 at the bottom and claims 3, 4, 5 and 6). However, the cysteine is always retained as an essential feature for dimerization.

Thus, it becomes clear that the inventors of WO 89/09788 considered only the conserved 7- or even only 6-cysteine region of this protein family as important for structure and activity. In addition, WO 89/09788 gives information about some amino acids within the conserved cysteine region, which are, according to the inventors of WO 89/09788, in addition to the cysteines, very important for the three-

dimensional folding and activity. Page 11 is referenced, wherein it is stated: "Note that these generic sequences have 6 and preferably 7 cysteine residues where inter- or intramolecular disulfide bonds can be formed and contain other critical amino acids influences the tertiary structure of the proteins".

In view of this information of the state of the art with regard to dimer proteins, a person skilled in the art would assume that monomer proteins could also be shortened at their N-terminus without losing activity. A lot was known with regard to dimer proteins which could easily be transferred to the corresponding monomer protein after the present inventors found that MP52 proteins are active without the intermolecular cysteine bond. Therefore, guidance with regard to amino acids critical for structure and function for the proteins of this family was available in the art and could easily be transferred to the corresponding monomer protein. Applicants also point out that US 5,658,882, states that "the first cysteine in the 7-cysteine structure characteristic of TGF-P proteins begins at nucleotide #577. The last cysteine ends at #879. Thus, it is expected that DNA sequences encoding active BMP-12 species will comprise nucleotides #577 to #879 of SEQ ID NO: 1" (see column 5, lines 60-65). In view of the extensive knowledge in the art at the time the present invention was made, applicants contend that one skilled in the art would be able to make and use the claimed monomer protein and request that this rejection be withdrawn.

In new claim 12, there are only four specific amino acids given which can be replaced with the cysteine which is responsible for the intermolecular cysteine bond. The present specification indicates that MP52 does not need an intermolecular cysteine bond to be active (page 2, lines 29-36). Thus, a person skilled in the art would assume that in this position any amino acid can be used which does not interfere with the formation of the three-dimensional structure of MP52. As is explained in the description on page 3, lines 25-26, the specific amino acids defined in claim 12 do not interfere with the three-dimensional structure since they are quite small.

Claims 1-4 and 6-10 were rejected under 35 USC §112, first paragraph, as lacking an adequate written description. As discussed above, extensive knowledge was available in the art regarding dimer members of the BMP protein family, which is a subfamily of the TGF-β superfamily. In *Falkner v. Inglis*, 79 USPQ2d 1001 (CAFC 2006), the essential regions of the sequences were known in the art but not recited in the application. The court held that the application met the requirements for written description since one of ordinary skill in the art would have possessed the required knowledge and a patent need not teach, and preferably omits, what is well known in the art. In the present situation, sequences for dimer members of the TGF-β superfamily were known in the art as were the regions critical for activity. Thus, applicants contend that the present application provides an adequate written

description of the claimed subject matter and request that this rejection be withdrawn.

Claims 1-3 and 6-10 were rejected under 35 USC §102(b) as anticipated by Mason. Mason does not suggest or disclose a monomer protein which induces differentiation of osteoblasts as measured by alkaline phosphatase activity. In view of the amendments to claim 1, applicants request that this rejection be withdrawn.

Claims 1-3 and 6-10 were rejected under 35 USC §102(b) as anticipated by Brunner. Brunner is directed to transforming growth factor β1 which inhibits proliferation of a variety of cells, stimulates anchorage independent growth of non tumorigenic fibroblasts, stimulates fibronectin and collagen synthesis and secretion, induces squamous cell differentiation and inhibits myogenic differentiation. Brunner does not suggest or disclose a monomer protein which induces differentiation of osteoblasts as measured by alkaline phosphatase activity. In view of the amendments to claim 1, applicants request that this rejection be withdrawn.

Claim 4 was rejected under 35 USC §102(b) as anticipated by U.S. Patent No. 5,658,882 (hereinafter '882). Claim 4 has been amended to depend from claim 1. The fragment disclosed in US 5,658,882, does not have biological activity. '882 only discloses that SEQ ID NO: 6 is a translated region of the DNA sequence of SEQ ID NO:5 (see column 16, Example 1). However, this DNA fragment is only a PCR fragment which was obtained when looking for novel members of the protein family using degenerated oligonucleotides. In doing so, a fragment was found which codes for part of the BMP-12 protein. As explained in column 5, lines 60-65, it is

expected that the active BMP-12 protein contains at least the 7-cysteine region: "The first cysteine in the seven cysteine structure characteristic of TGF-β proteins begins at nucleotide #577. The last cysteine ends at #879. Thus, it is expected that the DNA sequences encoding active BMP-12 species will comprise nucleotides #577 to #879 of SEQ ID NO: 1." However, the fragment of SEQ ID NO: 6 contains only two cysteines and, thus, cannot be active.

In addition, the fragment in SEQ ID NO: 6 does not contain the cysteine which is necessary for the intermolecular cysteine bond or instead of said cysteine an Ala, Ser, Thr or Val residue. When performing an alignment, the amino acids indicated in SEQ ID NO: 6 correspond to amino acids 39-63 of SEQ ID NO: 2 of the present application. Therefore, the amino acids of SEQ ID NO:6 do not contain the essential amino acid corresponding to position 83 of SEQ ID NO:2 of the present application. Claim 1 (and now claim 4) requires that this amino acid is included.

Furthermore, the fragment of SEQ ID NO: 6 differs from the corresponding region of SEQ ID NO: 2 of the present application at three positions. This fact is demonstrated in the following comparison of SEQ ID NO: 6 of US 5,658,882 with positions 39-63 of SEQ ID NO:2 of the present application. The differences are emphasized by bold letters:

P L **D** Y E A **Y** H C E G L C **D** F P L R S H L E P T N

P L **E** Y E A **F** H C E G L C **E** F P L R S H L E P T N

In view of the above amendments and discussion, applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 1-13 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

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